REMARKS

In the Action, the Examiner objected to the specification and claims due to various informalities, and also rejected all of the claims, namely claims 9-28, under 35 U.S.C. §112, first paragraph, for various reasons. Claims 9-28 were also rejected under 35 U.S.C. §112, second paragraph, as being indefinite for various reasons. None of the claims were rejected on the basis of prior art.

By this Amendment, claims 9-16, which were carried over from the previous application, have been canceled and thus withdrawn from the case. Thus, it is not believed necessary to respond to any of the specific objections to any of claims 9-16.

The specification was objected to due to the use of square brackets in many instances. That objection is noted and the brackets will be removed at a later date once allowance of one or more claims is secured.

Claims 17, 23, and 24 have been amended to correct various informalities, including the misspellings of "pylori" and "resistant."

In addition, the specification, as well as claims 17 and 18, have been amended in order to make it clear that the invention relates to the use of a "type III collagen" in the claimed complex, and not individual amino acids. It is clear from page 13 (line 4) of the specification that "collagen type III" is used in the invention. In this regard, information about commercial providers of such collagen was furnished previously, and it is not believed that anything further is needed here.

The above amendment to page 13 should clear up any misunderstanding relative to the use of "collagen type III" in the invention. Type III collagen comprises amino acids that are recited in claim 18, and are natural amino acids of proteins, whose concentrations are listed on page 13 of the specification. As can be noticed, "tryptophane" is not listed. The lack of tryptophane constitutes a specific characteristic of type III collagen. As a result, according to amended claims 17 and 18, an amino acid sequence is not provided nor identified by a SEQ number.

In view of the amendments to the specification and claims, it is submitted that persons of ordinary skill in the art would be able to make and reproducably practice the present invention. Thus, it is requested that the Examiner reconsider the rejection of the claims on that ground and pass the claims to issuance.

Claims 19 and 20 were objected to on the ground that they were not consistent with the specification. In particular, the Examiner refers to page 3, lines 3-4, where the "inefficacy" of *Helicobacter*-specific antibodies in protecting individuals is mentioned. However, since the term "and" is used in the description on page 3 to join "the production of antibodies" and "the production of endogenous interferon," this indicates that the complex components make it possible to induce both humoral and cellular responses. This is consistent with the full specification language on lines 1-4 of page 3, namely "the body must produce in addition to the specific humoral response, a cellular response in order to make up for the inefficacy of the antibodies in protecting the individual." When

the complete recitation from lines 1-4 on page 3 is taken into account, the meaning of the portion quoted by the Examiner in lines 3-4 can be correctly understood. As a result, it is requested that the Examiner reconsider the objection to claims 19-20 and pass them to issuance.

In the Office Action, the Examiner objected to the claims under §112 on the basis that there was insufficient evidence that the claimed vaccine is capable of inducing immunity against *Helicobacter* infection, for the reason that the experiments did not demonstrate an "art recognized standard" of improvement over the control of the efficacy of the vaccines. That ground of objection is not correct, however, since successful results obtained with the claimed vaccine are illustrated in the four examples set forth in the specification (pages 22-24). Tests for the detection of *H. pylori* were effected before and after the treatments, namely digestive endoscopy, biopsies plus rapid urease tests, and urea breath tests.

The Examiner also argues that the "art-recognized standard" for determination of *Helicobacter pylori* infection is endoscopy and evaluation of tissue samples. That position, however, is based on an "old" publication (Buck, 1986), and new up-to-date techniques are now used as explained in more recent publications. See, for example, "Helicobacter pylori, Basic Mechanisms to Clinical Cure 2000, R. H. Hunt and G.N.J. Tytgat (2000). A copy of relevant portions from the "Helicobacter pylori" publication are attached hereto as Exhibit A.

In Chapter 13 in the "Helicobacter pylori" publication (Exhibit A), it is indicated that "tests for the detection of *Helicobacter pylori* infection embrace a large battery of methods based on varying principles, and represent a model situation with no comparative analogy in infectious diseases" (Ex. A, p. 123). Also, in discussing serology, the publication states "since the appearance of the first serological tests for the detection of *Helicobacter pylori* infection in the mid-1980's, these tests have become more attractive because of their precision and the ability to obtain rapid results, their lower costs in comparison to UBT and stool antigen tests and their wide availability." (Ex A, p. 125.) In the discussion of the "urea breath test," the 2000 publication states: "the UBT is a non-invasive test of choice for detecting *H. pylori* infection with the greatest accuracy under pre- and post-treatment conditions." (Ex. A, p. 132.)

As seen from this recent publication, there are various techniques and information about additional tests for determination of *Helicobacter pylori* infections since the mid-1980s. It is submitted that persons or ordinary skill in the art would have been able to use them as standards and predict if protective immunity had been induced.

The Applicant also takes issue with the Examiner's comments concerning the unpredictability and effect of *Helicobacter pylori* vaccines. Although the Examiner cited documents in support of his position, the Applicant does not believe that the results and conclusions in these articles are generally recognized by scientists. New results obtained more recently by well-known researchers have reached the opposite conclusions.

In this regard, recent evidence indicates that vaccination against *Helicobacter pylori* is possible and supports the design of the claimed invention. For example, in the "Helicobacter pylori - Basic Mechanisms to Clinically Cure 2000," it is stated:

> "Immunization against *H. pylori* is possible, but our simple concept of removal by local IgA is wrong. Novel, probably cellular, mechanisms are involved." (Ex. A, pp. 189-190.)

Also, specific antigen is not necessary:

> "It is possible that modulating the immune response without specific defined antigen would also lead to an effective treatment of *Helicobacter* infection." (Ex. A, p. 195.)

Recent evidence also indicates that lipopolysaccharide (LPS) plays a role in biological interactions between bacteria and their hosts. (Ex. A, p. 198.)

As to the Examiner's comment concerning the term "immunomodulatory," it is clear that in the present application, that term means "which effect is immunomodulation." This concept is well known to persons of ordinary skill in the art and does not need to be specifically defined. See, for example, "Helicobacter Pylori, Basic Mechanisms to Clinical Cure 2000" (Ex. A, pp. 145-146). As a result, it is requested that the Examiner reconsider and withdraw the rejection of claim 17 under 35 U.S.C. §112 relative to its use of the term "immunomodulatory."

It is also submitted that the present specification provides substantial evidence that the claimed vaccine is capable of inducing protective immunity for prevention or treatment of *Helicobacter* infection. Although the Applicant has not provided data based

on animal studies, the Applicant has provided four specific examples based on actual use in humans. In general, animal models are not reliable because there are significant differences between the mucosal immune systems of mice and humans. Questions relating to an effective *H. pylori* vaccine should only be answered by clinical trials with human participants. "However, only rarely can the animal models fully mimic human disease; . . . the ultimate response will always come from testing the vaccine in humans." See, the attached article: Rappuoli R. et al., "Vaccines: From Concept to Clinic" (CVC Press 1999) (Exhibit B, pp. 8-9). This is precisely what the Applicant did in this case. The therapeutic effect of the claimed complex was tested in humans, and the examples in the specification (pp. 22-24) illustrate the results of those tests and show that the treatment was efficient.

An immunomodulatory vaccinal complex is considered to be a perspective approach. As stated in "Helicobacter Pylori, Basic Mechanisms to Clinically Cure 2000" (Ex. A, p. 146):

> *"Helicobacter* infection induces inflammation and stimulates an ineffective immune response...Immunomodulation may be an important and practical means of eliminating infections in large populations."

The claimed complex in accordance with the present invention pertains to a new generation of therapeutic methods. In this regard, the following quote from the Abstract

of Saldinger P.F., et al., "Journal of Physiology and Pharmacology," 48 Suppl. 4:59-65, (1997) is relevant (see Exhibit C):

> The immune effectors which prevent or cure infection with Helicobacter are not well understood and will need to be more clearly defined in order to improve vaccination strategies. Future developments will likely include the following: generation of new mucosal adjuvants without gastrointestinal toxicity; combination of two or three different antigens in order to ensure broader efficacy; use of different routes of administration such as nasal or rectal; coadministration of anti-Helicobacter treatment and vaccine; development of alternate vaccine methods which do not require a mucosal adjuvant, i.e. antigen expression by live carriers or by DNA vaccination; combination of different vaccination methods, for instance DNA vaccination followed by a mucosal boost.

As is often the case in the field of therapeutics, a combination of substances were found to be crucial for protective vaccination and/or treatment of *Helicobacter pylori* infection. Current evidence suggests a mechanism of action, as explained in the present specification (pages 14-19), but it is not completely known how this is achieved. In any event, the restored health of human patients in Examples 1-4 set forth in the present specification (pages 22-24) constitute substantial evidence of the efficiency of the complex as claimed in the present case.

In view of the foregoing, it is submitted that all of the claims remaining in the case, namely claims 17-28, are in proper form and patentably distinguish from the prior art. Additionally, it is believed that the subject matter of all of the claims is patentable

under the standards of 35 U.S.C. §112 for the reasons as stated above. Accordingly, allowance of the claims and passage of the application to issuance are respectfully solicited.

Respectfully submitted,

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"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

In the Specification:

Please replace lines 4-6 on page 13 with the following:

The collagen type III used is characterized by[:

a - Amino acid sequences containing] the following amino acid concentrations expressed in g/kg:

In the Claims:

Claims 9-16 have been cancelled.

Claims 17, 18, 23, 24, and 28 have been replaced with the following:

17. (Amended) An immunomodulatory and *anti-Helicobacter-specific* vaccine complex comprising:

(a) ribosomal ribonucleic acid extracted from bacteria selected from the group consisting of: *Helicobacter [pylon] pylori, Helicobacter hepaticus, Helicobacter coronari,* or a mixture thereof[.];

(b) [amino acid sequences from] a type III collagen[,]; and

(c) bacterial membrane fractions containing glycopeptides and/or lipopolysaccharides.

18. (Amended) The immunomodulatory and vaccine complex according to claim 17 wherein the [amino acid sequences from collagen comprise] type III collagen comprises amino acids selected from the group consisting of aspartic acid, hydroxyproline, threonine, serine, glutamic acid, proline, glycine, alanine, valine, methionine, isoleucine, leucine, tyrosine, phenylalanine, lysine, histidine, arginine, and mixtures thereof.

23. (Amended) The immunomodulatory and vaccine complex according to claim 17, for use against antibiotic-resistant *Helicobacter* bacteria [resisting] resistant to conventional treatments.

24. (Amended) The immunomodulatory and vaccine complex according to claim 18, for use against antibiotic-resistant *Helicobacter* bacteria [resisting] resistant to conventional treatments.